Welcome to issue 122 of Respiratory Research Review with focus on venous thromboembolic disease and PAH (pulmonary arterial hypertension).

Venous thromboembolic disease continues to be the third most common vascular cause of death after myocardial infarction and stroke, and arguably one of the most preventable. Patients with asthma and COPD may be at increased risk of developing a VTE, and when affected, have a higher mortality. A large Italian population-based study suggests that the mortality of VTE has reduced. This may be due to more awareness and better treatment or increasing diagnostics. In this context, it is interesting to reflect on the tenth edition of the ACCP (American College of Chest Physicians) guidelines, which now suggest that a subsegmental PE may not necessarily need to be treated. This raises the importance of severity and risk assessment. I believe that the European Cardiology Society guidelines, endorsed by the European Respiratory Society and available as a free downloadable app, are a big step forward. We review more evidence around risk stratification and the role of biomarkers, in particular copeptin. We are also reviewing an article from Leiden suggesting that anticoagulation for a cancer-related VTE event can be stopped when the cancer is cured.

More therapies for PAH are becoming available and our understanding of this illness improves. Selexipag, an oral prostacyclin receptor agonist, is joining the group of agents that will ameliorate this terrible disease. Marc Humbert suggests in his review of REVEAL data that the average survival has improved from 2.8 to 5.2 years. However, that is still not a satisfactory clinical outcome. In addition, several areas need more research – like the role of warfarin therapy, which may not be beneficial for patients with scleroderma-related pulmonary hypertension.

We hope you enjoy the selection of articles and are happy to receive feedback and discussion.

Kind regards
Professor Lutz Beckert
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COPD and risk of venous thromboembolism and mortality in a general population

Authors: Barvik T et al.

Summary: This research investigated the association between COPD and the risks of VTE and mortality in the general population. Spirometry was conducted in 8646 participants in the fifth (2001–2002) and sixth (2007–2008) surveys of the Tromsø study. During median follow-up of 6.2 years, 215 participants developed VTE. Those with COPD stage III/IV had a higher risk of secondary VTE than those with normal airflow (HR 2.05 [95% CI 1.02, 4.10]). Patients with COPD and VTE had a higher mortality rate than patients with COPD without VTE (50.2% vs. 5.6% per year).

Comment: The researchers of this study report on aspects of the Tromsø study recruiting about 8500 participants, with a mean age of 61 years, who all had detailed assessment on inclusion, including spirometry. Over the study period, 215 validated VTE episodes were reported, about half presenting with PE and about half with DVT alone. The authors speculated that the increased risk of VTE is possibly related to immobilisation, bronchial infection, right ventricular failure and hospitalisation. Bottom line: patients with GOLD stage III/IV COPD had a 1.6-fold increased risk of VTE. The presence of VTE was a strong predictor of all-cause mortality.


Abstract

Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy

Authors: Dentali F et al.

Summary: This large epidemiological study collected PE hospitalisation data for a population of ~13 million people living in Northwest Italy. There were 60,853 patients with PE identified giving overall crude incidence rates of 55.4 and 40.6 events per year per 100,000 inhabitants for women and men, respectively (p<0.001; statistical significance was lost after standardisation for age). There were significant increases in PE incidences for both genders over the study period, whereas in-hospital case fatality rates decreased significantly from 15.6% to 10.2% in women and from 17.6% to 10.1% in men; these decreases remained significant on adjustment for possible confounders.

Comment: This study is based on 13 million people from Northwest Italy. Over 11 years, the incidence of PE increased from 48 to 62 per 100,000 in woman and from 35 to 46 per 100,000 in men. The use of CTPA scanning increased from 22% to 59% in the period 2002–2012. The mortality rate of PE decreased from 7.6 to 6.6 per 100,000 in men and 6.0 to 4.8 per 100,000 in woman. Stavros Konstantinides wonders if this is related to better treatment in his editorial. Bottom line: it is possible that an ageing population and increased CT scanning contributed to the trend of an increasing PE incidence and decreased PE fatality.


Abstract

Trends in the management and outcomes of acute pulmonary embolism

Authors: Jiménez D et al.

Summary: Management and outcomes of 23,858 adults with acute symptomatic PE enrolled in the RIETE registry were reported. The authors reported the following trends over the evaluation period: 2001–2012. The mortality rate of PE decreased from 7.6 to 6.6 per 100,000 in men and 6.0 to 4.8 per 100,000 in woman. Stavros Konstantinides wonders if this is related to better treatment in his editorial the bottom line: while we are hoping this reduced mortality rate reflects better treatment, it may just be related to the increased detection of PE.

Reference: J Am Coll Cardiol 2016;67(2):162-70

Abstract

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Cohort study on the management of cancer-associated venous thromboembolism aimed at the safety of stopping anticoagulant therapy in patients cured from cancer

Authors: van der Hulle T et al.

Summary: This research followed 358 patients with cancer-associated VTE for the effect of cancer treatment, recurrent VTE, major haemorrhage and death. Anticoagulant treatment was continued until death in 207 patients, 12 received continued anticoagulation due to an alternative indication despite cure from cancer and 21 discontinued anticoagulation after major haemorrhage. Among patients who discontinued anticoagulation after cure from cancer (n=68), ten experienced symptomatic recurrent VTE (incidence rate 3.2 per 100 patient-years), seven of whom were also diagnosed with cancer relapse during follow-up. Among patients who stopped anticoagulant treatment despite active cancer (n=50), the incidence rate of recurrent VTE was 19 per 100 patient-years.

Comment: VTE may be the second largest cause of death in patients with cancer. The treatment is challenging as patients are at increased risk of recurrent VTE as well as bleeding. These authors from Leiden report on a cohort of 358 patients with cancer-related VTE. A total of 68 patients were cured of cancer and had no other indication for anticoagulation, so therapy was stopped. Of the ten patients, who had recurrent VTE, seven also had a relapse of their cancer. Bottom line: the VTE recurrence rate in patients cured of cancer is similar to the recurrence rate of unprovoked VTE; however, a further PE points towards relapsed cancer.

Reference: Chest; Published online Jan 13, 2016

Abstract

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Risk stratification of normotensive pulmonary embolism: prognostic impact of copeptin

Authors: Hellenkamp K et al.

Summary: These authors reported on 268 prospectively followed normotensive patients with PE from a single centre. Higher median copeptin levels were seen in the 5.6% of participants with an adverse 30-day outcome compared with those who had a favourable course (51.8 vs. 13.2 pmol/L, p=0.020), and the risk of an adverse outcome was significantly increased by a factor of 5.4 for participants with copeptin levels above the calculated optimal cutoff value of 24 pmol/L (p=0.005). The authors developed a biomarker-based strategy for risk stratification. No adverse outcomes were seen in patients with a high-sensitivity troponin T level <14 pg/mL or NT-proBNP (N-terminal pro-B-type natriuretic peptide) level <600 pg/mL (n=141). A copeptin level ≥24 pmol/L stratified patients with elevated high-sensitivity troponin T and NT-proBNP levels as intermediate-low and intermediate-high risk, with 5.6% and 20.0% experiencing adverse outcomes, respectively. This strategy classified more patients as low risk compared with the algorithm proposed by the 2014 European Society of Cardiology guidelines (52.8% vs. 17.5% [p<0.001]), and more intermediate-high risk patients experienced an adverse outcome (20.0% vs. 11.6%).

Comment: This article and editorial reflect on risk assessment using the PESI (Pulmonary Embolism Severity Index) or ePESI. It combines clinical information, cardiac dysfunction, troponin T and BNP biomarkers. A German group reports the risk assessment, investigation and outcomes of 268 patients with PE. They found that copeptin, the C-terminal end of the precursor protein of vasopressin, is a good predictor of adverse outcomes. Bottom line: when integrating copeptin in to the ePESI algorithm instead of an echocardiogram, it performs better than the original algorithm; more people are classified at low risk and less at high risk without an increase in adverse outcomes.


Abstract

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Antithrombotic therapy for VTE disease

Authors: Kearon C et al.

Summary: These authors present the latest CHEST Guideline and Expert Panel Report on managing VTE, including updated recommendations on 12 topics and three new topics. Long-term DOACs (direct oral anticoagulants) are recommended over vitamin K antagonists (grade 2B), and vitamin K antagonists over LMWHs (grade 2C), for patients with VTE but no cancer, whereas in patients with VTE and cancer, LMWHs are recommended over vitamin K antagonists (grade 2B) and DOACs (grade 2C). Inferior vena cava filters are not recommended for anticoagulant-treated VTE (grade 1B), and route compression stocking use is not recommended for DVT to prevent post-thrombotic syndrome (grade 2B). Clinical surveillance is recommended over anticoagulation in subsegmental PE and no proximal DVT when recurrent VTE risk is low (grade 2C), but anticoagulation is preferred over clinical surveillance when recurrence risk is high (grade 2C). For PE with hypotension, thrombolytic therapy is suggested (grade 2B), with systemic therapy preferred over catheter-directed thrombolysis (grade 2C). LMWHs are advised for VTE recurrence while on a non-LMWH anticoagulant (grade 2C), and an LMWH dose increase is recommended for recurrent VTE while receiving an LMWH (grade 2C).

Comment: John Heffner observed in his editorial that the tenth edition of the ACCP antithrombotic guidelines has over the last 20 years matured to become the ‘action’ arm of a funnel of knowledge, translating research findings into clinical practice. Several statements are important, like the consideration of aspirin after completion of a course of anticoagulation or the avoidance of vena cava filters in patients who can be safely anticoagulated. My favourite recommendation is the bottom line: in patients with subsegmental PE on a CTPA scan without DVT and with a low risk of recurrence, the guidelines suggest surveillance over anticoagulation.

Reference: Chest 2016;149(2):315–52

Abstract

Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

Long-term outcome of patients with chronic thromboembolic pulmonary hypertension

Authors: Delcroix M et al.

Summary: Data from prospective European registry patients with newly diagnosed CTEPH (chronic thromboembolic pulmonary hypertension) over a 24-month period were reported, comparing those treated operatively (n=404) with those who were not (n=275). The respective estimated 1-, 2- and 3-year survival rates were 93%, 91% and 89% in patients who underwent operations and 88%, 79% and 70% in nonoperatively managed patients; PAH-targeted therapy had no significant effects on these survival estimates. In operated and nonoperated patients, associations were seen between mortality and New York Heart Association functional class (relative risks 4.16 [CI 1.49, 11.62] and 4.76 [1.76, 12.88]), increased right atrial pressure (1.34 [0.95, 1.90] and 1.50 [1.20, 1.88]) and history of cancer (3.02 [1.36, 6.69] and 2.15 [1.18, 3.94]). Other factors correlated with mortality included PAH-targeted bridging pharmacotherapy, postoperative pulmonary hypertension, surgical complications and additional cardiac procedures in operated patients, and comorbidities such as coronary disease, left heart failure and COPD in nonoperated patients.

Comment: Between 0.4% and 9.1% of patients with an acute PE develop CTEPH, caused by nonresolving fibrothrombotic obstruction of the pulmonary arteries. The treatment of choice is pulmonary endarterectomy, which should only be performed in specialist centres. This report from the European registry incorporating 27 centres accounts for 679 patients with newly diagnosed CTEPH; 60% were operated on, 40% were not. The hospital mortality was less than 5%, and medical therapy with sildenafil or bosentan didn’t seem to improve survival. Bottom line: patients with operative management have significantly improved survival despite similar baseline haemodynamic severity at diagnosis.

Reference: Circulation 2016;133(9):859–71

Abstract
Effect of warfarin treatment on survival of patients with pulmonary arterial hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)

Authors: Preston IR et al.

Summary: This was an individual participant data meta-analysis for 1550 patients with idiopathic, heritable, anorexigen-associated PAH, 448 of whom had BMPR2 mutations. Compared with patients without BMPR2 mutations, those with such mutations had: i) a younger mean age at diagnosis (35.4 vs. 42.0 years [p<0.0001]); ii) greater mean pulmonary artery pressure (60.5 vs. 56.4 mm Hg [p<0.0001]); iii) greater pulmonary vascular resistance (16.6 vs. 12.9 Wood units [p<0.0001]); iv) lower cardiac index (2.11 vs. 2.51 L/min/m² [p<0.0001]); and v) a lower response rate to acute vasodilator testing (3% vs. 16% [p=0.0001]). Among patients with available survival data (n=1164), the presence of a BMPR2 mutation increased the risks of the composite of death or lung transplantation (adjusted HR 1.42 [95% CI 1.15, 1.75]) and mortality (1.27 [1.00, 1.60]); the increased risks did not differ significantly between men and women, but patients with a younger age at diagnosis had higher risks (consistent with the published literature and the precise mechanisms remain elusive). The authors of this diligently performed individual participant meta-analysis of 1550 patients found a BMPR2 mutation in 30% of patients. A BMPR2 mutation was found in 17% of sporadic and 82% of familial PAH. Bottom line: patients with a BMPR2 mutation present at a younger age, have more severe disease and are at increased risk of death.


Abstract

Outcomes of β-blocker use in pulmonary arterial hypertension

Authors: Bandypadhyay D et al.

Summary: This propensity-matched analysis reported on outcomes associated with β-blocker use in patients with pulmonary hypertension: data from 133 β-blockers users and 375 nonusers were included, and median follow-up was 78 months. No significant difference was seen between β-blocker users versus nonusers for mortality (adjusted odds ratio 1.13 [95% CI 0.69, 1.82]) or clinical worsening (0.96 [0.55, 1.68]). Furthermore, β-blocker users had shorter follow-up 6-minute walk test distance and similar follow-up New York Heart Association class than nonusers.

Comment: This report explores the role of β-blockers in PAH in a database of about 500 PAH patients. β-blockers increase mean pulmonary artery pressures at maximal exercise in healthy adults and have negative inotropic and chronotropic effects, which may impair exercise capacity. However, β-blockers may reverse right ventricular remodelling and dysfunction and have a general positive effect on the left ventricle. This single-centre study provides further data for the discussion, comparing about one-third of patients taking a β-blocker, mainly metoprolol, with nonusers. Bottom line: PAH patients taking a β-blocker had a similar survival, similar time to clinical worsening and a tendency to shorter walking distance.


Abstract
Selexipag for the treatment of pulmonary arterial hypertension

Authors: Sitbon O et al., for the GRIPHON Investigators

Summary: This phase 3 trial randomised 1156 patients with PAH to receive selexipag at individualised dosages (maximum 1600μg twice daily) or placebo. Compared with placebo, selexipag was associated with a significantly lower primary endpoint event rate (composite of death from any cause or PAH-related complication; 27.0% vs. 41.6%; HR 0.60 [99% CI 0.46, 0.78]), with disease progression and hospitalisation accounting for 81.9% of the events. No significant between-group difference was seen for the primary endpoint among patients who were on versus off treatment at baseline (including those who were receiving combination therapies). At study end, 100 selexipag recipients and 105 placebo recipients had died from any cause, and the respective adverse event-related discontinuation rates were 14.3% and 7.1% – the most common events among selexipag recipients were consistent with the known adverse effects of prostacyclin (i.e. headache, diarrhoea, nausea and jaw pain).

Comment: The current therapeutic targets in the management of PAH are the endothelin, nitric oxide and prostacyclin pathways. Several oral agents interact with the endothelin and nitric oxide pathways – the therapies for prostacyclin pathways have normally been given intravenously, subcutaneously or via inhalation. Many patients have never received this therapy. In this phase 3 study, the authors report on the effects of selexipag, an orally available prostacyclin receptor agonist. Treatment with selexipag almost halved the risk of disease progression, including in the one-third of participants already receiving sildenafil and bosentan.

Bottom line: selexipag looks like a promising new oral agent for treating PAH.


Abstract

Five-year outcomes of patients enrolled in the REVEAL registry

Authors: Farber HW et al.

Summary: These researchers reported on REVEAL registry enrollees aged ≥3 months with newly and previously diagnosed WHO group 1 PAH; survival analyses were conducted according to functional class and other subgroups in adult patients. One-year survival differences between previously and newly diagnosed patients (90.4% vs. 86.3%) were maintained out to 5 years (65.4% vs. 61.2%). Previously diagnosed patients in functional classes I–IV had respective estimated 5-year survival rates of 88.0%, 75.6%, 57.0% and 27.2%, compared with 72.2%, 71.7%, 60.0% and 43.8% for newly diagnosed patients.

Comment: This final review is also based on data from the ~3000 patients in the REVEAL registry comparing the survival of patients previously diagnosed with PAH with the survival of about 700 patients newly diagnosed with PAH. One key finding is that the 5-year survival of patients newly diagnosed with PAH was 61%, compared with survival of previously diagnosed PAH of 65%. Prior to specific treatment, the 5-year survival was 34%. Survival is worse in patients presenting in stage III/IV. Bottom line: overall, the survival of patients with PAH has improved with targeted therapy; however, the overall prognosis is still poor.


Abstract